AWARD NUMBER:

W81XWH-14-1-0615

TITLE: A Multimodal Evaluation of the Comparative Efficacy of Yoga versus a Patient-Centered Support Group for Treating Chronic Pain in Gulf War Illness

PRINCIPAL INVESTIGATOR: Peter Bayley, PhD

RECIPIENT: Palo Alto Veterens Institute for Research
Palo Alto, CA 94304

REPORT DATE: October 2016

TYPE OF REPORT:

Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
October 2016	Annual	29 Sept 2015- 28 Sept 2016

4. TITLE AND SUBTITLE

A Multimodal Evaluation of the Comparative Efficacy of Yoga versus a Patient-Centered Support Group for Treating Chronic Pain in Gulf War Illness

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-14-1-0615

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Peter Bayley, PhD – Peter.Bayley@va.gov
Rachael Cho, MSEd – Rachael.Cho@va.gov

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Palo Alto Veterens Institute for Research
3801 Miranda Ave
Palo Alto, CA 94304

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

The primary objective is to investigate yoga for the treatment of chronic pain in veterans with Gulf War Illness (GWI). A secondary objective is to provide veterans with skills in yoga breathing, postures, and meditation that can be used to promote health and well-being. One hundred (100) patients with GWI will be recruited and assigned with equal probability to one of two treatment groups: yoga treatment group or a pain management (control) group. During this reporting period, 26 veterans enrolled into the study, for a total of 51 veterans enrolled; the fifth study cohort of yoga and pain management (control) classes is currently in progress.

15. SUBJECT TERMS
Chronic Pain, Gulf War Illness, Chronic Illness, Veterans, Chronic Disease, Chronic Pain, Disease Attributes, Nervous System Diseases, Neurologic Manifestations, Pain, Pathologic Processes, Signs and Symptoms.

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
U	U	U	UU	12	19b. TELEPHONE NUMBER *(include area code)*

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18

TABLE OF CONTENTS

	Page No.
1. Introduction	3
2. Keywords	3
3. Accomplishments	3
4. Impact	7
5. Changes/Problems	7
6. Products	9
7. Participants & Other Collaborating Organizations	10
8. Special Reporting Requirements	11
9. Appendices	11

1. **INTRODUCTION:** Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.

Many military personnel who participated in the Gulf War in 1990-1991 reported negative health consequences subsequent to their deployment, the most prevalent involving a triad of symptoms that include fatigue, pain, and cognitive disturbances, commonly referred to as "Gulf War Illness" (GWI). No clear, unifying patho-physiological disease process or effective treatment has yet been identified for GWI. Results from a diverse spectrum of research studies support the view that veterans with GWI are medically ill, but that the physiological abnormalities that contribute to their illness are not currently well understood nor sufficiently treated by conventional medicine. While the cause of GWI remains unknown, a potential link between GWI and autonomic nervous system (ANS) dysregulation has been suggested. Yoga has been suggested to exert its therapeutic effects through adjusting imbalances in the ANS. In addition, yoga has been shown to be clinically effective in treating many of the physical symptoms typically found in GWI including chronic pain and fatigue. As chronic pain is perhaps the most prevalent and debilitating symptom of GWI, we have chosen pain as the primary target of our intervention. To date, no improvements in pain have been reported in any clinical trial involving GWI and no published studies have investigated yoga as an intervention for GWI.

The primary objective is to investigate yoga for the treatment of chronic pain in veterans with GWI and determine if the health-related benefits of yoga persist after the termination of the treatment plan. A secondary objective is to provide veterans with skills in yoga breathing, postures, and meditation that can be used to promote health and well-being. One hundred (100) patients with GWI will be recruited and assigned with equal probability to one of two treatment groups: a yoga treatment group or a pain management (control) group. The control group has been carefully designed to control for many features of the yoga intervention. Patients in both groups will attend weekly classes for 10 weeks, followed by six months of follow-up testing. Monitoring will include periodic measures of pain, fatigue, quality of life, and ANS function.

2. **KEYWORDS:** Provide a brief list of keywords (limit to 20 words).

Chronic Pain, Gulf War Illness, Chronic Illness, Veterans, Chronic Disease, Chronic Pain, Disease Attributes, Nervous System Diseases, Neurologic Manifestations, Pain, Pathologic Processes, Signs and Symptoms.

3. **ACCOMPLISHMENTS:** The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction.

What were the major goals of the project?

The overarching goals include:
1. Develop a manualized yoga treatment protocol for veterans with chronic pain. (100% complete)
2. Develop a manualized behavioral treatment protocol for veterans with chronic pain. (100% complete)
3. Conduct a randomized clinical trial (N=100) to evaluate the efficacy of yoga in reducing chronic pain in Gulf War veterans as compared to a pain management (control) group. (In progress)
4. Determine if the health-related benefits of treatment persist after termination of the program. (To be completed during the data analysis, report findings phase)

What was accomplished under these goals?

During this reporting period, the goals encompassed four specific objectives. Each of these objectives involved subtasks and milestones, which are described below.

1. Major Task 1: Prepare standard protocols for study.
    a. Subtask 1: Prepare manualized treatments for study.
        i. Milestone: Develop a manualized yoga treatment protocol for Veterans with chronic pain.
            - 100% complete.
        ii. Milestone: Develop a manualized behavioral treatment protocol for Veterans with chronic pain.
            - 100% complete.
2. Major Task 2: Study preparation.
    a. Subtask 1: Obtain regulatory approval.
        i. Milestone: Receive approval from the Stanford IRB, in addition to the Human Research Protection Office (HRPO).
            - 100% complete.
    b. Subtask 2: Identify one or more Community-Based Outpatient Clinics (CBOC) to use as a second site.
        i. Milestone: Identify a suitable local CBOC.
            - Currently not applicable; VA Palo Alto continued/s to be the most productive recruitment site of Veterans into the study
    c. Subtask 3: Recruit and train study staff.
        i. Milestone: Hire study staff.
            - 100% complete for hiring study coordinator and instructors for yoga and behavioral interventions.
            - Hired a replacement behavioral intervention instructor, database manager, and postdoctoral researcher; recruited an additional volunteer for the yoga treatment group.
    d. Subtask 4: Facilitate training, supervision, and fidelity checks with new staff.
        i. Milestone: Maintain trained and available study staff throughout the duration of the trial.
            - Ongoing.
    e. Subtask 5: Set up Access (now REDCap) database.
        i. Milestone: Create a functioning Access database, complete with fillable forms for data entry.
            - 100% complete.
            - Microsoft Access will be phased out of the VA computer network in 2017. For this reason, we proactively set up a functioning database using REDCap and completed transferring information from our existing Access database, in advance of the VA's transition.
3. Run randomized controlled study.
    a. Subtask 1: Conduct study and report findings.
        i. Milestone: Consent, screen, and enroll first participant.
            - 100% complete. Enrolled the first participant on 06/01/15; began running the study on 06/16/15.
            - Recruited participants through various media (flyers, mass mailings, targeted recruitment via clinics, Facebook, web-based recruiting, etc.) and Gulf War-specific patient lists (Gulf War Registry and Defense Manpower Data Center (DMDC)). Obtained two other targeted patient lists of Gulf War era patients seen at VA Palo Alto Health Care System during fiscal year 2015 from data analysts from VA Palo Alto.
            - Screened potential participants using telephone screening waiver of consent (total: 442 local Veterans + 483 non-local Veterans).
            - Consented, screened, and enrolled participants into the study and commenced the study (51 Veterans).
        ii. Milestone: Begin study.
            - Evaluated and randomly assigned participants to one of the two treatment groups: Yoga and Pain Management (control) Group.
                - The fifth study cohort is currently in progress.
            - Assessed participants at 2, 4, 6, 8, 10-week timeframe.
                - Cohort A (06/16/15-08/18/15); Cohort B (09/15/15-11/17/15); Cohort C (02/02/16-04/05/16); Cohort D (06/21/16-08/23/16); Cohort E (10/11/16-12/13/16)
            - Complete follow-up assessments at 2, 4, and 6-month timeframe.

- Cohort A (week 18 – 10/13/15; week 26 – 12/08/15; week 34 – 02/02/16)
- Cohort B (week 18 – 01/12/16; week 26 – 03/08/16; week 34 – 05/03/16)
- Cohort C (week 18 – 05/31/16; week 26 – 07/26/16; week 34 – 09/20/16)
- Cohort D (week 18 – 10/18/16; week 26 – 12/13/16; week 34 – 02/07/16)
- Cohort E (week 18 – 02/07/17; week 26 – 04/04/17; week 34 – 05/30/17)

iii. Milestone: Collect data at the end of treatment and follow-up assessments.
- Completed end of treatment and follow-up assessments for Cohorts A, B, and C.
- Completed end of treatment for Cohort D in August 2016; follow-up assessments for Cohort D are in progress.
- Will complete end of treatment for Cohort E the week of 12/13/16 and follow-up assessments thereafter.

4. Data analysis, report findings
   a. Subtask 1: Coordinate with Data Manager for monitoring data collection.
      i. Milestone: Report results from data analyses.
      - Not yet applicable but actively maintained and monitored data collection.
      - Created a comprehensive checklist to ensure completeness of all patient files.

What opportunities for training and professional development has the project provided?

- 09/2016 – Dr. Bayley presented a poster at the Symposium on Yoga Research at the Kripalu Institute for Yoga & Health in Stockbridge, Massachusetts. ("Yoga Via Telehealth Provides Comparable Satisfaction and Health Improvements to In-Person Yoga." Schulz-Heik, R. J., Mahoney, L., Stanton, M.V., Cho, R.H., Moore-Downing, D., Avery, T., Varni, J.M., Collery, L.M., & Bayley P.J.)

- 08/2016 – Dr. Bayley and Rachael Cho attended a meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses in San Francisco, California.

- 05/2016 – Dr. Bayley presented a VA Webinar on behalf of the War Related and Injuries Study Center (WRIISC) titled "Yoga as Treatment for Chronic Post-Deployment Health Conditions". The audience composed of 400+ researchers, clinicians, social workers nationwide.

- 05/2016 – Rachael Cho participated in a workshop on Good Clinical Practice hosted by Stanford's Department of Psychiatry & Behavioral Sciences and Stanford Center of Clinical Research. The workshop focused on good documentation practices and maintaining accurate regulatory documents.

- 09/2015 – Dr. Bayley presented a poster at the Symposium on Yoga Research at the Kripalu Institute for Yoga & Health in Stockbridge, Massachusetts. ("Preliminary results from a clinical yoga program for veterans: evidence for efficacy in treating musculoskeletal pain." Stanton, M.V., Cho, R.H., Mahoney, L., Moore-Downing, D., Avery, T., Varni, J.M., Collery, L.M., & Bayley P.J.)

  This abstract received the Swami Kuvalyananda Scholarship Award in recognition of excellence and innovation in yoga research.

- 10/2016; 07/2016; 04/2016; 01/2016; 10/2015 – Dr. Bayley and Rachael Cho participated in the quarterly Gulf War Teleconferences organized by Victor Kalasinsky, Senior Program Manager of Gulf War Illnesses/Military Environmental Exposures at the VA's Office of Research and Development to collaborate with other Gulf War researchers.

How were the results disseminated to communities of interest?

Nothing to report. To prevent possible bias, data from this single-blind clinical trial will not be analyzed until the last patient has finished the treatment phase; all assessors for follow-up testing are blind and will remain blind until the last patient has finished follow-up assessments.

What do you plan to do during the next reporting period to accomplish the goals?

1) Study preparation.
   a. Identify one or more Community-Based Outpatient Clinics (CBOC) to use as a second site and recruit Veterans for that site.
      - Continue collaborating with a General Medicine Physician at the San Jose CBOC and possibly the Fremont CBOC, and recruit Veterans for a cohort at a CBOC to begin in 2017.
   b. Recruit and train study staff.
      - Train new postdoctoral researcher to lead the behavioral intervention.
   c. Facilitate training, supervision, and fidelity checks with new staff.
      - Maintain available study staff throughout the duration of the trial.
2) Run randomized controlled study.
   a. Continue to conduct study and report findings.
      - Continue to recruit participants through various media (flyers, mass mailings, targeted recruitment via clinics, Facebook, web-based recruiting, etc.), in addition to targeted patient lists.
        - National: recruit participants by collaborating with other researchers who focus on Gulf War Veteran research and may be connected to local GW Veterans.
        - Local: recruit participants at CBOC's through targeted advertisements.
        - VA Palo Alto: partner with specific groups to increase focused recruitment: Physical Medicine & Rehabilitation clinic, the Front Office, Canteen (hospital cafeteria). In addition, utilize targeted patient lists of Gulf War era patients seen at VA Palo Alto Health Care System during fiscal year 2015 from data analysts at VA Palo Alto.
      - Consent, screen, and enroll participants into the study. Minimize time between when Veterans show interest and a new cohort starts. Begin Cohort F, slated to commence in January or February 2017.
      - Evaluate and randomly assign participants to one of the two treatment groups: Yoga and Pain Management Wellness Group. Begin new cohorts.
      - Assess participants at 2, 4, 6, 8, 10-week timeframe.
        - Cohort E (Week 2 – 10/18/16; Week 4: 11/1/16; Week 6: 11/15/16; Week 8: 11/29/16; Week 10: 12/13/16)
      - Collect data for the end of treatment and follow-up assessments at 2, 4, and 6-month timeframe.
        - Cohort D (Week 18 – 10/18/16; Week 26: 12/13/16; Week 34: 02/07/17)
        - Cohort E (Week 10 – 12/13/16; Week 18: 02/07/17; Week 26: 04/04/17; Week 34: 05/30/17)
      - In all phases of the study, retain participants who have consented and enrolled in the study.
        - Remind participants of classes on a weekly basis and of appointments in advance.
        - Keep participants engaged in the classes.
3) Data analysis, report findings.
   a. Maintain monitoring of data collection.
      - Not yet applicable but actively maintain and monitor data collection.
      - Continue to use our comprehensive checklist to ensure completeness of all patient files.

4. **IMPACT:** Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:

What was the impact on the development of the principal discipline(s) of the project?

Nothing to report.

What was the impact on other disciplines?

Nothing to report.

What was the impact on technology transfer?

Nothing to report.

What was the impact on society beyond science and technology?

Nothing to report.

5. **CHANGES/PROBLEMS:** The Project Director/Principal Investigator (PD/PI) is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:

Changes in approach and reasons for change

During this reporting period, a community based outpatient clinic (CBOC) was not identified for use as a second study site as projected; this was due to the fact that VA Palo Alto continued/s to be the most productive recruitment site of Veterans into the study. We have currently enrolled five cohorts of patients at VA Palo Alto into the study.

Actual or anticipated problems or delays and actions or plans to resolve them
Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

Study recruitment was/is anticipated to continue to be a challenge in this study. The specific recruitment challenge is that Veterans must have been enlisted in the military during the first Gulf War (1990-1991). During the last reporting period, we employed several forms of mass mailings. This recruitment method generally had relatively low yields.

- In May 2015, the study's information was publicized in a national War Related Illness and Injury Study Center (WRIISC) newsletter.
    - 475 Veterans contacted the study (7 local Veterans); 5 were eligible; 1 consented,

screened, and enrolled in the study.

- In June/July 2015, VA SF/UCSF collaborator, Dr. Linda Chao, mailed 241 Gulf War I Veterans in the greater Bay Area; 85 letters (35%) were returned to the sender.
    - 12 Veterans replied; 8 were eligible; 1 consented, screened, and enrolled in the study.
- In July 2015, Markots Marketing sent 11,383 postcards to Veterans between the ages of 45-85.
    - 11 Veterans contacted the study; 2 were eligible; 1 consented, screened, and enrolled in the study.

During the current reporting period, we obtained four patient lists: two Gulf War-specific patient lists (Gulf War Registry and Defense Manpower Data Center (DMDC)) and two targeted patient lists of Gulf War era patients seen at VA Palo Alto Health Care System during fiscal year 2015.

- Gulf War Registry: The study team received a list of 1,087 local Veterans from the national Gulf War Registry and permission to contact the Veterans directly. In February and March 2016, the study team mailed an IRB-approved letter, study flyer, response card, and a business reply envelope to 1,087 local Veterans; 449 (41%) were "returned to sender." Despite using a highly targeted list, the database was not as fruitful as anticipated, due to obsolete patient contact information. Two Veterans who enrolled in the study heard about the clinical trial through this mailing.
- Defense Manpower Data Center (DMDC): In October 2015, the study team requested the names and addresses of local Gulf War veterans ≤ 60 miles of VA Palo Alto (zip code: 94304) from the Defense Manpower Data Center (DMDC). The study team received the list in May 2016 and mailed an IRB-approved letter, study flyer, response card, and a business reply envelope to 4,108 Veterans. As of October 20, 2016, 669 (16%) have been "returned to sender;" however, 11 Veterans who enrolled in Cohorts D and E heard about the clinical trial through this mailing.
- The PI and Study Coordinator networked with data specialists at VA Palo Alto to obtain two lists of patients:
    1) Patients who have a diagnosis of chronic pain (ICD-9 338.2) and whose period of service is labeled as "Persian Gulf War;"
    2) A comprehensive list of Gulf War era patients seen at VA Palo during FY2015.

    The study team is working to verify the Veterans' dates of service in the VA Computerized Patient Record System (CPRS) and will submit an IRB amendment to contact the Veterans directly, instead of collaborating with the patients' primary care providers to contact the patients.

Going forward, we anticipate that recruitment will continue to be a challenge. To address this challenge, we will continue to employ a combination of multiple recruitment methods to *actively* advertise our study:

- Follow up with Veterans who, for various reasons, were previously unable to join our cohorts.
- Recruit weekly at VA Palo Alto Farmer's Market and in the lobby of the main hospital building.
- Present our study to VA clinicians/medical care teams and providing study flyers for their clinics.
- Place study flyers in high-traffic areas of VA Palo Alto on a weekly basis.
- Utilize social media, in addition to websites, to broaden our reach and have an online presence.
- Collaborating with the Veteran Service Organizations (VSO) and various other veteran groups.

Changes that had a significant impact on expenditures

Nothing to report.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Significant changes in use or care of human subjects

Nothing to report.

Significant changes in use or care of vertebrate animals.

Nothing to report.

Significant changes in use of biohazards and/or select agent

Nothing to report.

6. PRODUCTS: List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."

- **Publications, conference papers, and presentations**
  Report only the major publication(s) resulting from the work under this award.
  Journal publications.

Nothing to report.

- **Books or other non-periodical, one-time publications**

Nothing to report.

- **Other publications, conference papers, and presentations**.

Nothing to report.

- **Website(s) or other Internet site(s)**

Nothing to report.

- **Technologies or techniques**

Nothing to report.

- **Inventions, patent applications, and/or licenses**

Nothing to report.

- **Other Products**

Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	Peter Bayley, PhD
Project Role:	Project Director
Nearest person month worked:	2
Contribution to Project:	Oversees project management, personnel training, study regulatory activity.
Name:	Rachael Cho
Project Role:	Research Assistant/Study Coordinator
Nearest person month worked:	12
Contribution to Project:	Ms. Cho is the Study Coordinator and performs work in the areas of patient screening, personnel management, marketing, and study regulatory activity.
Name:	Louise Mahoney
Project Role:	Co-Investigator
Nearest person month worked:	2
Contribution to Project:	Developed yoga treatment manual with team of yoga therapists and consultants. Lead patients in the yoga group and managed the group.
Name:	Jessica Schienle
Project Role:	Pain Support Group Leader
Nearest person month worked:	1
Contribution to Project:	Edited and developed the manual for the control condition (Behavioral Pain Intervention). Lead patients in the control group.
Name:	Linda Collery
Project Role:	Yoga Leader
Nearest person month worked:	1
Contribution to Project:	Lead participants in yoga classes. Data input and patient recruitment.
Name:	Danae Moore-Downing
Project Role:	Yoga Leader
Nearest person month worked:	2
Contribution to Project:	Lead participants in yoga classes. Data input and patient recruitment.
Name:	Stephan Kim
Project Role:	Clinical Research Assistant I
Nearest person month worked:	6
Contribution to Project:	Set up and maintained database and oversaw data input.
Name:	Stephanie Chan
Project Role:	Therapy Group Leader
Nearest person month worked:	1
Contribution to Project:	Lead participants in the control group. Data input and patient recruitment.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

GRANT 1 I01 RX001485-01 (PI: Bayley)
07/01/2015 – 06/28/2019
2.40 calendar
VA RR&D Merit Review
$1,014,173
Breathing Meditation Intervention for Post-Traumatic Stress Disorder

The major goals of this project are to investigate the efficacy of breathing meditation for treating symptoms of PTSD in Veterans and to compare it to the standard of care (cognitive processing therapy).

A previously pending grant is now active:

GRANT I01HX001678-1 (PI: McAndrew / Co-I: Bayley)
07/01/2015 – 06/30/2019
1.2 calendar
VA HSR&D Merit Review
$1,499,865
WRIISC as a Model of Care for Chronic Multisymptom Illness

This observational prospective study will examine the relationship between the degree of concordance in illness perceptions between Gulf War Veterans (GWVs) with chronic multi-symptom illness (CMI) and providers and health outcomes.

What other organizations were involved as partners?

Defense Manpower Data Center (DMDC) Reporting System
Seaside, CA
Collaboration to assist with patient recruitment. DMDC is a branch of the Department of Defense and maintains data, such as names, address, and phone numbers on Veterans. We completed a 7-month application process and obtained a list of 4,108 Veterans ≤ 60 miles of VA Palo Alto (zip code: 94304) from the Defense Manpower Data Center (DMDC) in May 2016.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: For collaborative awards, independent reports are required from BOTH the Initiating PI and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to **https://ers.amedd.army.mil** for each unique award.

QUAD CHARTS: If applicable, the Quad Chart (available on https://www.usamraa.army.mil) should be updated and submitted with attachments.

9. APPENDICES: Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.